1: Nature 1994 Apr 28;368(6474):856-9

Comment in:
- Nature. 1994 Apr 28;368(6474):812

Antigen-specific human antibodies from mice comprising four distinct genetic modifications.

Lonberg N, Taylor LD, Harding FA, Trounstine M, Higgins KM, Schramm SR, Kuo CC, Mashayekh R, Wymore K, McCabe JG, et al.

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Human sequence monoclonal antibodies, which in theory combine high specificity with low immunogenicity, represent a class of potential therapeutic agents. But nearly 20 years after Kohler and Milstein first developed methods for obtaining mouse antibodies, no comparable technology exists for reliably obtaining high-affinity human antibodies directed against selected targets. Thus, rodent antibodies, and in vitro modified derivatives of rodent antibodies, are still being used and tested in the clinic. The rodent system has certain clear advantages; mice are easy to immunize, are not tolerant to most human antigens, and their B cells form stable hybridoma cell lines. To exploit these advantages, we have developed transgenic mice that express human IgM, IgG and Ig kappa in the absence of mouse IgM or Ig kappa. We report here that these mice contain human sequence transgenes that undergo V(D)J joining, heavy-chain class switching, and somatic mutation to generate a repertoire of human sequence immunoglobulins. They are also homozygous for targeted mutations that disrupt V(D)J rearrangement at the endogenous heavy- and kappa light-chain loci. We have immunized the mice with human proteins and isolated hybridomas secreting human IgG kappa antigen-specific antibodies.

PMID: 8159246 [PubMed - indexed for MEDLINE]

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